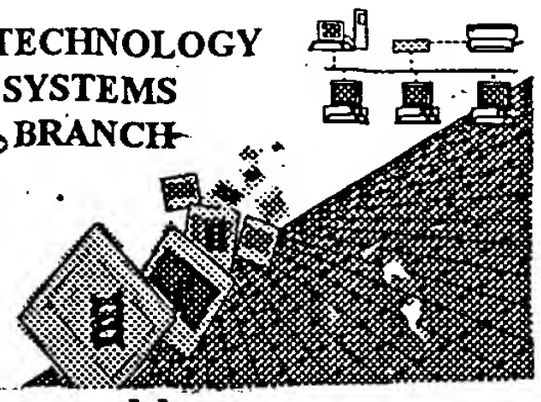
0360/010

BIOTECHNOLOGY SYSTEMS BRANCH



01PE

CRF Problem Report

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Application Serial Number: 09|780,014
Filing Date: 02|09|2001
Date Processed by STIC: 4|7|03

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Revised 04/01/2003

□CProjectData□□□□OBiocompatible Material Composition Adaptable to Diverse Therapeuitc Indications□1849.16102-A CIP 3
US 09/780,014□2001-02-09□□□□□□□ÿÿ□□□□CProtein1Sequence□□□□□1□Artificial SequenceILGPA
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wide variety of different sizes and different mixtures of the above-mentioned constituents dependent on the status of remodeling during the metabolic RCT cascade.

The key enzyme involved in the RCT pathway is LCAT. LCAT is produced mainly in the liver and circulates in plasma associated with the HDL fraction. Cholesteryl ester transfer protein (CETP) and another lipid transfer protein, phospholipid transfer protein (PLTP) contribute to further remodeling the circulating HDL population. CETP can move cholesteryl esters made by LCAT to other lipoproteins, particularly ApoB-containing lipoproteins, such as VLDL. HDL triglycerides can be catabolized by the extracellular hepatic triglyceride lipase, and lipoprotein cholesterol is removed by the liver via several mechanisms.

Each HDL particle contains at least one copy (and usually two to four copies) of ApoA-I. ApoA-I is synthesized by the liver and small intestine as preproapolipoprotein which is secreted as a proprotein that is rapidly cleaved to generate a mature polypeptide having 243 amino acid residues. ApoA-I consists mainly of 6 to 8 different 22 amino acid repeats spaced by a linker moiety which is often proline, and in some cases consist of a stretch made up of several residues. ApoA-I forms three types of stable structures with lipids: small, lipid-poor complexes referred to as pre-beta-1 HDL; flattened discoidal particles containing only polar lipids (phospholipid and cholesterol) referred to as pre-beta-2 HDL; and spherical particles containing both polar and nonpolar lipids, referred to as spherical or mature HDL (HDL_3 and HDL_2). Most HDL in the circulating population contain both ApoA-I and ApoA-II (the second major HDL protein) and are referred to herein as the AI/AII-HDL fraction of HDL. However, the fraction of HDL containing only ApoA-I (referred to herein as the AI-HDL fraction) appear to be more effective in RCT. Certain epidemiologic studies support the hypothesis that the AI-HDL fraction is antiartherogenic. (Parra et al., 1992, Arterioscler. Thromb. 12:701-707; Decossin et al., 1997, Eur. J. Clin. Invest. 27:299-307)